REMARKS

Reconsideration is requested.

Claims 107-146 are pending. Claims 136-146 have been added and find support in pending claims 108, 109, 111, 115, 116, 120, 123, 125, 128, 131 and 133, respectively, as well as the specification. Claims 136-146 are similar to pending claims 108, 109, 111, 115, 116, 120, 123, 125, 128, 131 and 133 with the additional recitation of sequence identifiers.

More specifically, the specification and claims have been revised to include a reference to the wild-type *P. pyralis* luciferase sequence (SEQ ID NO: 1) as described in the art as SEQ ID NO: 2 of WO95/25798 referred to at page 8, lines 19-33 of the present specification, except that the mutated amino acid "Xaa" at position 354 in SEQ ID NO: 2 of WO95/25798 is stated as the wild-type glutamate (see WO95/25798, page 2, second paragraph). The wild-type *Luciola cruciata* luciferase sequence (SEQ ID NO: 2) of the present claims and attached Sequence Listing corresponds to SEQ ID NO: 2 of EP0524448 (the published specification from European Patent Application No. 92110808.0 referred to at page 8, lines 19-33 of the present specification). The wild-type *L. lateralis* luciferase sequence (SEQ ID NO: 3) of the present claims and specification corresponds to SEQ ID NO: 8 of EP0524448 (see above). Wild-type *L. mingrelica* luciferase (SEQ ID NO: 4) of the present specification and claims is described in WO95/25798 (see above), where its amino acid sequence was considered to be known in the art (see, for example, page 1, third paragraph, and page 3, final paragraph). The amino acid sequence of SEQ ID NO: 4 of the present specification and claims was obtained from SwissProt database accession No. Q26304 (with reference to

Devine *et al.*, 1993, Biochim. Biophys. Acta 1173: 121-132). Finally, the amino acid sequence for wild-type *E. coli* adenylate kinase (SEQ ID NO: 5) of the present specification and claims was obtained from Brune *et al.* (1985; of record, and cited on page 5, first paragraph of the present specification). One of ordinary skill in the art will appreciate that the specification describes the sequences of the attached Sequence Listing as they generally included the state of knowledge of the art as wild-type sequences. No new matter has been added.

The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added.

Claims 117 and 125 have been corrected above, as suggested by the Examiner, to obviate objection to same stated on page 2 of the Office Action dated October 23, 2006. The undersigned's oversight in not earlier correcting the claims in this regard is regretted and the Examiner's helpful reminder for obviating the objection is acknowledged with appreciation.

The Section 112, second paragraph, rejection of claims 108-109, 111, 115-116 and 120-135 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above, the following as well as the remarks of record.

The Examiner is understood to believe that the position recitations of the rejected claims require recitation of a reference sequence. The same is not believed to be required for one of ordinary skill to appreciate the metes and bounds of the rejected claims, for the reasons of record. The Examiner is further requested to see the Capon v. Eshhar, Appeal No. 03-1480, -1481, Fed. Cir. (August 12, 2005) http://fedcir.gov/opinions/03-1480.pdf, wherein the Court held as follows:

> The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh. Id at page 15.

The Examiner's reliance on GenBank Accession No. BAA14303 (Miyamoto,K., Nakahigashi,K., Nishimura,K. and Inokuchi,H. "Isolation and characterization of visible light-sensitive mutants of Escherichia coli K12" J. Mol. Biol. 219 (3), 393-398 (1991)) to allegedly show an uncertainty in the sequence positions of E. coli. adenylate kinase is noted. See pages 3-4 of the Office Action of October 23, 2006. Specifically, the Examiner asserts that the sequence of GenBank Accession No. BAA14303 describes position 87 and 107 of the polypeptide as alanine and glycine, respectively as opposed to the art of record which describes the amino acids of these positions as proline and leucine, respectively.

The undersigned notes however that the sequence of GenBank Accession No. BAA14303 is an N-terminal truncated sequence and that one of ordinary skill would readily appreciate that position 1 of the sequence of GenBank Accession No. BAA14303 corresponds to position number 108 of the sequence of E. coli adenylate kinase. The following comparison of E. coli adenylate kinase (Accession number P69441 (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=60392511)[1])

[1] Citing to at least the following: Brune,M., Schumann,R. and Wittinghofer,F."Cloning and sequencing of the adenylate kinase gene (adk) of Escherichia coli" Nucleic Acids Res. 13 (19), 7139-7151 (1985); Chung,E., Allen,E., Araujo,R., Aparicio,A.M., Davis,K., Duncan,M., Federspiel,N., Hyman,R., Kalman,S., Komp,C., Kurdi,O., Lew,H., Lin,D., Namath,A., Oefner,P., Roberts,D., Schramm,S. and Davis,R.W. Direct Submission Jan-1997; Blattner,F.R., Plunkett,G. III, Bloch,C.A., Perna,N.T., Burland,V., Riley,M., Collado-Vides,J., Glasner,J.D., Rode,C.K., Mayhew,G.F., Gregor,J., Davis,N.W., Kirkpatrick,H.A., Goeden,M.A., Rose,D.J., Mau,B. and Shao,Y., "The complete genome sequence of Escherichia coli K-12" Science 277 (5331), 1453-1474 (1997); Hayashi,K., Morooka,N., Yamamoto,Y.,

with the sequence of GenBank Accession No. BAA14303 (underneath and in italics) demonstrates what will be readily recognized by one of ordinary skill in the art.

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  1 mriillgapg agkgtqaqfi mekygipqis tgdmlraavk sgselgkqak dimdagklvt
 61 delvialvke riaqedcrng flldgfprti pqadamkeag invdyvlefd vpdelivdri
              GenBank Accession No.  BAA14303        1 efd vpdelivdri

121 vgrrvhapsg rvyhvkfnpp kvegkddvtg eelttrkddq eetvrkrlve yhqmtaplig
    vgrrvhapsg rvyhvkfnpp kvegkddvtg eelttrkddq eetvrkrlve yhqmtaplig

181 yyskeaeagn tkyakvdgtk pvaevradle kilg
    yyskeaeagn tkyakvdgtk pvaevradle kilg
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The above demonstrates therefore that positions 87 and 107 of the E. coli adenylate kinase polypeptide are not included in the sequence of GenBank Accession No. BAA14303. The applicants have not reviewed the disclosure of Miyamoto,K., Nakahigashi,K., Nishimura,K. and Inokuchi,H. "Isolation and characterization of visible light-sensitive mutants of Escherichia coli K12" J. Mol. Biol. 219 (3), 393-398 (1991)) as the Examiner has not cited or relied on the same in support of the rejection. The above

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Fujita,K., Isono,K., Choi,S., Ohtsubo,E., Baba,T., Wanner,B.L., Mori,H. and Horiuchi,T. "Highly accurate genome sequences of Escherichia coli K-12 strains MG1655 and W3110" Mol. Syst. Biol. 2, 2006 (2006); Bardwell,J.C. and Craig,E.A. "Eukaryotic Mr 83,000 heat shock protein has a homologue in Escherichia coli" Proc. Natl. Acad. Sci. U.S.A. 84 (15), 5177-5181 (1987); Miyamoto,K., Nakahigashi,K., Nishimura,K. and Inokuchi,H. "Isolation and characterization of visible light-sensitive mutants of Escherichia coli K12" J. Mol. Biol. 219 (3), 393-398 (1991); Link,A.J., Robison,K. and Church,G.M. "Comparing the predicted and observed properties of proteins encoded in the genome of Escherichia coli K-12" Electrophoresis 18 (8), 1259-1313 (1997); Frutiger,S., Hughes,G.J., Pasquali,C. and Hochstrasser,D.F. Direct Submission FEB-1996; Wilkins,M.R., Gasteiger,E., Tonella,L., Ou,K., Tyler,M., Sanchez,J.C., Gooley,A.A., Walsh,B.J., Bairoch,A., Appel,R.D., Williams,K.L. and Hochstrasser,D.F. "Protein identification with N and C-terminal sequence tags in proteome projects" J. Mol. Biol. 278 (3), 599-608 (1998); Reinstein,J., Brune,M. and Wittinghofer,A. "Mutations in the nucleotide binding loop of adenylate kinase of Escherichia coli" Biochemistry 27 (13), 4712-4720 (1988); Reinstein,J., Schlichting,I. and Wittinghofer,A. "Structurally and catalytically important residues in the phosphate binding loop of adenylate kinase of Escherichia coli" Biochemistry 29 (32), 7451-7459 (1990); Munier-Lehmann,H., Burlacu-Miron,S., Craescu,C.T., Mantsch,H.H. and Schultz,C.P. "A new subfamily of short bacterial adenylate kinases with the Mycobacterium tuberculosis enzyme as a model: A predictive and experimental study" Proteins 36 (2), 238-248 (1999); Muller,C.W. and Schulz,G.E. "Structure of the complex between adenylate kinase from Escherichia coli and the inhibitor Ap5A refined at 1.9 A resolution. A model for a catalytic transition state"

suggests however that GenBank Accession No. BAA14303 does not describe E. coli adenylate kinase, as appears to be asserted by the Examiner.

The rejection of claim 127 noted in § [7] of the Office Action dated October 23, 2006 is obviated by the above amendment to delete the objected-to phrase.

Withdrawal of the Section 112, second paragraph, rejection of claims 108-109, 111, 115-116 and 120-135 is requested.

The Section 112, first paragraph "new matter", rejection of claims 117-119, 125-127 and 122-135 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following and the remarks of record.

In addition to the remarks of record, the applicants submit that claims 117-119 find descriptive basis in the original claims 15-17, respectively, and in the specification at page 5, lines 6-9, and page 8, lines 1-5 and lines 7-12. For designating adenylate kinase as the "undesired protein", there is a basis at page 1, lines 4-6 of the specification and in original claim 7. Present claim 125 additionally finds a basis at page 5, lines 6-19. For the remaining claims 126, 127 and 133-135, the same bases apply.

The above amendment to recite a *Luciola* luciferases mutation at position 356 is described, for example on page 8, lines 19-22 of the present specification of thermostable luciferases described in European patent application No. 92110808.0 and WO95/25798 provides support for the rejected claims 108-109, 115-116 and 120-135.

Withdrawal of the Section 112, first paragraph "new matter", rejection is requested.

J. Mol. Biol. 224 (1), 159-177 (1992); and Muller,C.W. and Schulz,G.E. "Crystal structures of two mutants of adenylate kinase from Escherichia coli that modify the Gly-loop" Proteins 15 (1), 42-49 (1993).

The Section 112, first paragraph "written description" rejection of claims 107-135 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the remarks of record as well as the following comments.

The applicants submit that a person of ordinary skill in the art would appreciate that luciferases from various species are well known and are highly conserved (see, for example, alignment of luciferase sequence from various species in Fig. 2 of Ye *et al.*, 1997, of record). The mutant luciferases recited in the present claims support a genus having a common structure which determines their common luciferase activity.

Furthermore, the person of ordinary skill in the art would appreciate that adenylate kinases are highly conserved in structure and activity. By way of example, the applicants submit the attached Saint Girons *et al.* (1987; J. Biol. Chem. 262: 622-629) and request the Examiner to note in the first paragraph of the introduction on page 622 that the primary structure of five types of muscle adenylate kinase (from pig, human, calf, chicken and rabbit) "revealed an extremely high degree of homology".

The *E. coli* adenylate kinase isolated by Saint Girons *et al.* (1987) similarly had a "rather high degree of homology" with pig muscle adenylate kinase (page 628, right hand column).

Further evidence is provided by the attached Kishi *et al.* (1987, J. Biol. Chem. 262: 11785-11789), who found that two bovine adenylate kinases were highly homologous to *E. coli* adenylate kinase and were able to functionally complement an *E. coli* adenylate kinase mutant, as they expected from the degree of homology (see paragraph flanking left and right hand columns, page 11787).

As elaborated on page 4, line 17 to page 5, line 4 of the present specification, suitable mutants of such adenylate kinases can be produced and identified using techniques well known to a person of ordinary skill in the art.

The present claims are submitted to be supported by an adequate written description and withdrawal of the Section 112, first paragraph "written description" rejection is requested.

The Section 112, first paragraph "enablement", rejection of claims 107-135 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the remarks of record as well as the following.

The applicants again submit that one of ordinary skill in the art would not require demonstration of alteration of every amino acid to make and use the presently claimed invention. The above-noted Capon v. Eshhar is believed to be relevant in this regard as well. The claims are submitted to be supported by an enabling disclosure and withdrawal of the Section 112, first paragraph, rejection of claims 107-135 is requested.

The Section 103 rejection of claims 107-108, 110-115 and 120-124 over Backman (EP 373962), Squirrell (WO 96/02665), Squirrell (WO 96/22376) and Gilles (PNAS (1986) 83: 5798-5802), as stated in § [12] of the Office Action dated October 23, 2006, is traversed. The Section 103 rejection of claims 117-119 and 125-127 over Backman (EP 373962), Squirrell (WO 96/02665), Squirrell (WO 96/22376) and Gilles (PNAS (1986) 83: 5798-5802) and Novagen 1997 Catalog stated in § [13] of the Office Action dated October 23, 2006, is traversed. The Section 103 rejection of claims 107, 109-114, 116 and 128-132 over Backman in view of Squirrell (WO 96/02665), Kajiyama (Biochemistry 32:13795-13799) and Gilles (PNAS (1986) 83: 5798-5802) stated in §

[14] of the Office Action dated October 23, 2006, is traversed. The Section 103 rejection of claims 117-119 and 133-135 over Backman (EP 373962), Squirrell (WO 96/02665), Kajiyama (Biochemistry 32:13795-13799), Gilles (PNAS (1986) 83: 5798-5802), Novagen and Kiel, stated in § [15] of the Office Action dated October 23, 2006, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the remarks of record and the following further comments.

The applicants submit that the Examiner has combined the cited art with an impermissible use of hindsight. There was no motivation in the cited art to have combined the references as collected by the Examiner and even if so combined there was no suggestion in the same to make the presently claimed invention. The Examiner's previous assertions of where motivation exists in the cited art is submitted, with due respect, to be based, in a circular fashion, on an assertion that because the prior art documents can be combined to allegedly arrive at the invention there was motivation to do so. The applicants submit, again with due respect to the Examiner, that the Examiner has failed to show that there is a teaching, suggestion or motivation either explicitly or implicitly in the cited prior art references to combine or modify them. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (MPEP 2143.01), which the Examiner has failed to demonstrate.

Withdrawal of the Section 103 rejections is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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